REMARKS

STATUS OF THE CLAIMS

Claims 1-28 and 36-38 are pending in this application. Claim 1 has been amended. Following entry of the amendments claims 1-28 and 36-38 will be pending and at issue.

ELECTION/RESTRICTIONS

Applicant notes that the Examiner has agreed with the Applicant's traversal and has withdrawn the requirement to elect a particular percentage of genes in a Table and the genes that comprise that percentage. The Examiner indicated on page 3 of the Office Action that "Table 69 was elected as a species, and the other tables are withdrawn as being drawn to non-elected species." Thus, the Examiner has maintained the requirement of election of a single Table as a species under MPEP §806.04, and has accepted the election of Table 69.

SPECIFICATION

The Examiner noted the use of trademarks in the application. Applicant has capitalized and indicated trademarks noted by the Examiner, as requested.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 24-28 and 36-38 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner indicated that Table 69 has been amended to recite that the listed genes correspond to SEQ ID NOs 2240-2265, and has indicated that these 25 SEQ ID NOs do not correspond to the listed genes in the Table since there are only 14 genes in the Table. In an earlier response, the Applicant included a footnote where the first sequence is shown (SEQ ID NO. 1, at Table 5), which the Examiner suggested during the last interview and agreed would be sufficient to clarify the correspondence between the SEQ ID NOs and each row of the Table. As explained in this footnote, its description applies to all Tables (including Table 69), and it explains the correspondence between the horizontal rows in the Tables and the SEQ ID NOS listed in the Table heading of each Table. For further clarification, Applicant has also

added a footnote to Table 69 to ensure that the correspondence between the Table and the SEQ ID NOS is clear.

To further explain the correspondence in this response, each set of related, consecutive sequences (e.g., nucleotide sequences encoding a protein or homologous nucleotide sequences) is assigned to a single row in the Table, and the next such set is assigned to the following row in the Table going down the rows in the Table. Thus, in general, for each row in a Table (or for each gene), there is both a nucleotide sequence and the corresponding amino acid sequence. The amino acid sequences were provided for the Examiner's reference and for ease in searching. In a few cases, the amino acid sequence was unavailable so only the nucleotide sequence appears. For example, for Table 69a, SEQ ID NO. 2240 is a nucleotide sequence that corresponds to the first row, or gene name MGC5466. In this case, there was only a nucleotide sequence available, so there is only one sequence for this row. SEQ ID NOS 2241 and 2242 are the nucleotide and amino acid sequences, respectively, for the second row, gene name Wnt5A. SEQ ID NOS 2243 and 2244 are the nucleotide and amino acid sequences, respectively, for the third row, gene name KIAA0476. SEQ ID NOS 2245 and 2246 are the nucleotide and amino acid sequences, respectively, for the fourth row, gene name ITPR1. SEQ ID NOS 2247 and 2248 are the nucleotide and amino acid sequences, respectively, for the fifth row, gene name TCF2. In Table 69b, for the first row, SEQ ID NO 2249 corresponds to gene name MGC5466. Again, for this gene, there was only a nucleotide sequence available, so there is only one sequence for this row. SEQ ID NOS 2250 and 2251 are the nucleotide and amino acid sequences, respectively, for the second row of Table 69b, gene name CHAF1A. SEQ ID NOS 2252 and 2253 are the nucleotide and amino acid sequences, respectively, for the third row of Table 69b, gene name CDS2. SEQ ID NOS 2254 and 2255 are the nucleotide and amino acid sequences, respectively, for the fourth row of Table 69b, gene name IER3. In Table 69c, SEQ ID NOS 2256 and 2257 are the nucleotide and amino acid sequences, respectively, for the first row, gene name PPFIA3. SEQ ID NOS 2258 and 2259 are the nucleotide and amino acid sequences, respectively, for the second row of Table 69c, gene name COPEB. SEQ ID NOS 2260 and 2261 are the nucleotide and amino acid sequences, respectively, for the third row of Table 69c, gene name FOS. SEQ ID NOS 2262 and 2263 are the nucleotide and amino acid sequences, respectively, for the fourth row of Table 69c, gene name JUNB. SEQ ID NOS 2264 and 2265 are the nucleotide and amino acid sequences, respectively, for the fifth row of Table 69c, gene name ZFP36.

For the Examiner's quick reference, the correspondences are shown below.

Gene Symbol	SEQ ID NOS
Table 69a	
MGC5466	2240
Wnt5A	2241, 2242
KIAA0476	2243, 2244
ITPR1	2245, 2246
TCF2	2247, 2248
Table 69b	
MGC5466	2249
CHAF1A	2250, 2251
CDS2	2252, 2253
IER3	2254, 2255
Table 69c	
PPFIA3	2256, 2257
COPEB	2258, 2259
FOS	2260, 2261
JUNB	2262, 2263
ZFP36	2264, 2265

Applicants respectfully submit that the there is a clear correspondence between the SEQ ID NOs, and this correspondence has been even further clarified given this explanation and the footnotes in the specification. If the Examiner still finds this unclear, Applicant requests that the Examiner first contact the Applicant's representative by phone (650 335 7185) for clarification before preparing any further Office Action addressing this issue..

The Examiner also indicated that he searched GenBank for the GenBank IDs listed in Table 69, and found that they do not appear to exist. Applicant respectfully disagrees. Applicant searched each GenBank number and each one does exist. Applicant respectfully suggests that the Examiner refer to the National Center for Biotechnology Information (NCBI) website, http://www.ncbi.nlm.nih.gov/ that is most commonly used for such searches by persons of ordinary skill in the art. Applicant suggests that the Examiner choose in the "Search" drop down box the "Gene" database, and Applicant suggests searching that database for the Genbank ID. Applicant notes that in some instances, the Official Symbol that appears in the top link may be a different Symbol than the one listed in Table 69. For example, when searching for the Genbank ID U90904 for Gene Symbol MGC5466, the first link is to Official Symbol NIPA2, but this link indicates that Other Aliases for this gene include "MGC5466." Thus, this description makes it clear that this is the correct link for that gene. Applicant also notes that in some cases,

the proper link is not the first link shown. For example, when searching for GenBank ID AB007945 for KIAA0476, the top link is to a discontinued record, but the second link to DENND4B indicates that Other Aliases include KIAA0476, making it clear that this is the proper link for this gene. If the Examiner still has difficulty finding the appropriate gene records given the description above, Applicant requests that the Examiner first contact the Applicant's representative by phone for clarification before preparing any further Office Action addressing this issue.

Applicant further notes that Applicant provided multiple identifiers, besides the GenBank ID, that can each easily be used to locate the gene information for each gene. For example, again returning the "Gene" database of the NCBI website, one of ordinary skill in the art would be aware that it is possible to search the Gene Symbol. For example, the Symbol "Wnt5A" can be searched in the "Gene" database to produce the appropriate gene record. In the same manner, one can search the long gene name, such as "transcription factor 2, hepatic," in the Gene database. Similarly, at the NCBI website, one can search the "Unigene" database (instead of the "Gene" database) for the Unigene identifiers provided. Thus, the relevant records for each gene are, and were at the time of filing, very readily accessible to persons of ordinary skill in the art in various different manners. Applicant submits that this material is not new matter..

Applicant respectfully requests withdrawal of this ground of rejection. If the Examiner still has any remaining questions regarding this or needs any further clarification, Applicant requests that the Examiner contact Applicant's representative by phone to discuss this.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 24-28 and 36-38 were rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite because the Examiner stated that the GenBank IDs in the Tables do not exist and the SEQ ID NOs do not correspond to the number of genes in the Table. As explained in detail above, the GenBank IDs do exist and the SEQ ID NOs do correspond to the genes in the Table. Thus, it is clear what subject matter is claimed and what is to be searched. Applicant respectfully requests withdrawal of this ground of rejection.

REJECTIONS UNDER 35 U.S.C. § 101

Claims 1-28 and 36-38 were rejected under 35 U.S.C. § 101 as allegedly being unpatentable because the claimed invention is directed to non-statutory subject matter. The

Examiner stated that the instant claims do not produce a tangible final result. Applicant respectfully submits that the step of recording a listing of genes does provide a tangible final result. The Examiner stated that "it is unclear if that recording is accessible to the user," and the Examiner suggested some language regarding the listing being in a "user-readable format." Without agreeing with the rejection, but in the interested of expediting prosecution, the Applicant has amended the claims to recite "recording a listing of the subset of genes identified in a user-readable format," as suggested by the Examiner. Support for this amendment is found throughout the specification as filed, e.g., within the various tables of the specification that display or record, in a user-readable format (e.g. in the provided Tables), listings of identified subsets of genes within the concordance sets identified. The specification also provides numerous identifiers providing links to the genes recorded in a user-readable format. Thus, Applicant requests withdrawal of this rejection.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-23 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Backert et al. (Int. J. Cancer (1999) Volume 82, pages 868-874) in view of Bertucci et al. (Human Molecular Genetics (2000) Volume 9, Number 20, pages 2981-2991). Applicant traverses this ground of rejection.

The cited prior art references do not teach all of the elements of the claims. The Examiner contends that the Backert et al. teaches "a first reference set of expressed genes," "a second reference set of expressed genes," "a concordance set of expressed genes" and a "subset of genes within said concordance set." Applicant respectfully disagrees.

Backert explains that he begins with a "set of 588 human cDNAs with fragments of genes coding for proteins of different functional classes arrayed on nylon membranes" that was used for hybridization. Backert, p. 870, left side, bottom. The labeled cDNA probes were synthesized from mRNA of cell lines derived from normal and carcinomatous cell lines. *See Id.* Backert further explains that the "median values calculated for each group were then compared, and genes whose median expression was at least 3-fold larger or smaller than that in the 'normal' cell group were *selected for further testing* (Table II)." *Id.* at p. 870, right side (emphasis added). Thus, via the Atlas array methods described in Backert, he selects the 10 genes of Table II that are then used in his further testing. He then describes "further testing" of these 10 genes in his

description of his verification of the 10 genes using Northern blotting/RT-PCR techniques. Backert, p. 871, right side, second full paragraph ("analysis of 588 genes in Atlas array has led to detection of 10 consistent differences in expression, 6 of which were confirmed in Northern blot or RT-PCR"). Thus, Backert verified the array data using Northern blot/RT-PCR experiments, in which he found that 6 of the 10 genes shown in Table II were altered consistently. Backert, p. 870, left side.

The Examiner has equated the normal cells of Backert with the "first sample" of the claimed invention, the carcinomatous cells of Backert with the "second sample," and the 10 selected genes of Table II of Backert with the "first reference set." The Examiner found the Northern blot/RT-PCR verification to be an identification of a second reference set (the same 10 genes) from a third and fourth sample (the same cell lines used above), to produce a concordance set (the 6 genes). Applicant respectfully disagrees. First, the claim requires a step of "identifying a second reference set," but there was no "identification" of a second reference set that took place in Backert, since the identification had already occurred. The Northern blot/RT-PCR experiments were simply used as a verification of that identification. Second, there is no identification of a second set independent of the first set. The Examiner argued that the experiments were conducted independently and one set does not control over the second set in Backert. However, this is incorrect given that Backert's verification starts with the exact same set of 10 genes of Table II, and then verifies that set. The two sets are directly linked since they are *the exact same set* as no identification of a second set ever occurs.

The Examiner indicated that the Northern blot/RT-PCR experiment "obtained different results (i.e., a different reference set) and only verified 6 of the 10 gene alterations." Applicant respectfully submits that this is incorrect. As Backert makes clear various times in the reference, he uses the Atlas array to select the 10 genes for further testing, including the Northern blot analyses. Backert, p. 870 ("median values calculated for each group were then compared, and genes whose median expression was at least 3-fold larger or smaller than that in the 'normal' cell group were *selected for further testing* (Table II)") (emphasis added). He then goes on to perform Northern blot analyses of these 10 identified genes. He does not use the Northern blot analysis to independently conduct an analysis of the samples to identify a new or "second reference set" of genes with altered expression which is then combined with the array data set (e.g., "first reference set") of 10 genes to ultimately identify a concordance set between the two

reference sets (e.g., the 6 genes). Instead, he simply starts with the 10 genes identified by the array analysis and verifies expression of those 10 using Northern blot techniques. Table II makes this clear by showing the same 10 genes identified via the array experiments are also analysis via Northern blot/RT-PCR. The caption of Figure 1 also makes this clear by explaining that the Figure shows "Northern blots with RNA obtained from the tested cell lines, *with the fragments of the identified genes*," so he is testing the identified 10 genes. Backert, Figure 1 caption (emphasis added). This is further made clear by Table I in which he lists all of the probes used in the Northern blots, which correspond again with those 10 genes. Thus, there is never any identification of a second reference set as originally claimed, much less a second set independent of the first set.

Though Applicant disagrees with the Examiner's statements, in the interest of expediting prosecution, the Applicant has clarified the claim language. The claim recites "identifying a second reference set of expressed genes that includes at least one gene that is not included in the first reference set, said second reference set consisting of genes that are differentially expressed between a third sample and a fourth sample, at least one of which originates from a different source than said first and second samples, wherein said third and fourth samples differ with respect to said phenotype." As stated above, Backert discloses no step of "identifying a second reference set." Even assuming *arguendo* that the verification in Backert using Northern blot/RT-PCR experiments was an identification of a second set, that second set does not include "at least one gene that is not included in the first reference set." As explained above, the second set to which the Examiner points is the same set, and Table II makes clear (by showing the results side-by-side) that the exact same genes are examined via Northern blot/RT-PCR.

Further, the claim has been amended to recite that at least one of the third and fourth samples "originate from a different source than said first and second sample." The Examiner admitted that "Backert et al. uses the same cell lines" in both the array and Northern blot/RT-PCR analyses. Office action, p. 10. Thus, this claim element is not met.

The Examiner also pointed to the experiments regarding the human tissue, stating that these also produce a second independent reference set since the Examiner finds the results of the human tissue experiment "did not depend on the results of the cDNA array experiment," but instead obtained a different reference set. Office Action, p. 10. Applicant respectfully disagrees. Backert again makes clear various times in the reference that the same 10 genes are examined in

the human tissue experiments, and explains that there were "only 2 correct positives out of 10 detected in the cell lines. Backert, p. 871, right side, third full paragraph. Again, these human tissue experiments are a part of the "further testing" of the 10 genes that Backert describes. Backert, p. 870. Table II further clarifies that only those 10 genes were analyzed in the human tissue experiments. In addition, the same probes shown in Table I are used with the Northern blotting performed in the human tissue experiments. The caption of Figure 3 further explains that the Figure shows "tissue expression of genes whose altered expression was found in the cell lines," or in other words, the 10 selected genes. Backert, Figure 2 caption p. 872. Therefore, the human tissue disclosure of Backert fails to disclose "identifying a second reference set of expressed genes that includes at least one gene that is not included in the first reference set." Again, there is no identification of a second reference set regarding the human tissue as this is just another verification of the 10 genes.

Even assuming *arguendo* that the verification in Backert using the human tissue was an identification of a second set, that second set does not include "at least one gene that is not included in the first reference set," as the same 10 genes are used in both sets in Backert. Further, in the case of the human tissue verification of the 10 genes, only 2 genes were verified, which the Examiner calls the concordance set. However, the claim still requires "identifying a subset of genes within said concordance set," and there is no disclosure in Backert of identifying a subset of the 2 genes.

Backert explains numerous times that his goal is to show that the cDNA array method is useful in correctly identifying changes in gene expression. Backert, Abstract ("Our data show that the cDNA array method permits a correct identification of changes in gene expression with relative accuracy"); *Id.* at p. 873, left side, last paragraph ("In conclusion, our results show that the cDNA array permits a straightforward and in more than 50% of cases, a correct identification of differences in gene expression between different cell lines."). The Northern blot analyses in both the cell lines and human tissue are nothing more than methods for verification that the array techniques worked, rather than an independent identification of a reference set of genes with altered expression. Backert's title further reinforces that the article is focused on array techniques. Backert, Title ("Differential Gene Expression in Colon Carcinoma Cells and Tissues Detected with a cDNA Array").

With regard to the second reference, Bertucci, the Examiner maintains that Bertucci teaches "a first correlation coefficient, correlating for said genes within said subset a first expression differential between said first and second samples to a second expression differential between third and fourth samples, exceeds a predetermined value." In the second full paragraph of the right column on page 2987 of Bertucci, it is reported that a correlation coefficient is used to verify experimental results and is used to measure reproducibility of differential expression between two samples that are the same. Thus, it is not clear how the Bertucci's correlation coefficient could be used to select a subset of genes such that the correlation coefficient exceeds a predetermined value, where the coefficient correlates between samples from which reference sets are created that lead to a concordance set, from which the subset is identified. This is a complex correlation, and there is no description in Bertucci of how to accomplish anything like this. Even if Bertucci is relied on by the Examiner only for his correlation coefficient, it still must be clear to one of ordinary skill in the art from reading Bertucci exactly how to apply his correlation coefficient to the disclosure of Backert to produce the claimed invention. In this case, one of ordinary skill would not have known how to apply Bertucci's brief mention of a correlation coefficient to Backert's description of array data to produce the claimed invention.

Accordingly, the combination of Backert and Bertucci fails teach all of the elements of claim 1, and so cannot render independent claim 1 obvious, nor the claims that depend therefrom (claims 2-22). Therefore, withdrawal of this ground of rejection is respectfully requested.

Claims 12 and 13 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Backert et al. in view of Bertucci et al. and further in view of Young et al. (US Publication No. 2005/0255588 A1). Claims 12 and 13 depend from and incorporate all of the elements of claim 1. Therefore, claims 12 and 13 cannot be rendered obvious by the cited art for at least the reasons described above regarding claim 1. Accordingly, Applicant requests withdrawal of this rejection of claims 12 and 13.

In conclusion, a *prima facie* case of obviousness has not been presented by the Office. Therefore, withdrawal of this ground of rejection of claims 1-23 is respectfully requested.

Applicant notes that no prior art has been cited against claims 24-28 and 36-38. Applicant respectfully submits that the rejections of these claims under sections 112 and 101 have been overcome. Thus, Applicant requests that these claims be allowed.

CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicant's representative at (650) 335-7185.

Respectfully Submitted,
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